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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,391	08/24/2001	Xiao Tong	PC10790A	4934

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/938,391	TONG ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *12-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I claims 1-11 in Paper No. 15 is acknowledged. The traversal is on the ground(s) that all groups of the claims relate to polynucleotides sequences associated with regulation of angiogenesis and uses. Therefore it is reasonable and would not present an undue burden on office to keep all groups to gather in the instant application. This is not found persuasive because DNA, protein, antibodies and transgenic animals are structurally and functionally distinct products, which have different uses. Furthermore search of one (for example antibodies) would not lead to other (transgenic animals). Therefore there is serious burden to examine all the groups as one invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-36 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-11 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well-established utility.

The instant claims are drawn to an isolated DNA sequence, which encodes an endostatin-like polypeptide. The specification asserts the present invention relates to novel polynucleotide sequences, which encode the angiogenesis inhibitor endostatin, and more particularly, the canine angiogenesis inhibitor (spec. page 1, para.1). At best the specification teaches that addition of proposed canine-endostatin polypeptide inhibited the stimulating effect to of bFGF on CPAE

cells **in-vitro** (spec. page 72). The specification fails to disclose that nucleic acid sequences as claimed encodes a polypeptide that inhibit angiogenesis in a canine.

The instant invention is not considered to have a specific and/or substantial utility, since the instant specification fails to establish that that the disclosed polynucleotide sequences encodes an amino acid which inhibit angiogenesis explicitly or implicitly as putatively considered by the instant specification. The asserted ensostatin activity is mere hypotheses, since no biological function has been established. The specification fails to disclose a functional assay that would enable one skill in the art how to evaluate the biological activity of canine-endostatin. In addition the specification fails to establish any nexus between the inhibitions of stimulating effect to of bFGF on CPAE cells in-vitro with anti-angiogenic activity in in-vivo. The official sequence search reveled that the disclosed nucleotide sequence matches with a sequence related to human XVIII collagen but with 60.7% sequence similarity (AN:AF018082). Further inspection of the comparison shows limited if any areas of conservation between the two sequences.

The state of antiangiogenesis art is in very early stages of development. The tumor blood vessels proliferate 20-2000 times faster than any normal endothelium in an adult as the result hypoxia and variety of other uncharacterized stimuli. The net balance of pro and anti-angiogenic factors determine, whether new blood vessels are formed or not. Furthermore, not all parts of growing solid tumors participate in angiogenesis at the same time due to complex network of cytokines and angiogenic factors produced in a tumor. There are significant inter and inter-species variations in the tumor cell and tumor blood vessel micoenviornment, therefore great care should be taken in the extrapolation of in-vitro data to a in-vivo situation. More information on target epitopes density and distribution and coagulation status in experimental animal and cancer patients is required for the proper interpretations (Molema et al, Biochem, Pharmcol. 55:1939-45, 1999, see page 1941, 1993 col.1). Angiogenesis is multi factorial process that involves degradation of basement membrane, migration and proliferation of capillary EC cells and formation of three-dimensional capillary tubes. In-vitro cell migration assay is mere a prescreening method that further requires testing in a standard in-vivo model. Although number of factors are know to interfere with one or more of the steps required for angiogenesis in-vitro, it is essential to test these substances using in-vivo assay to ensure that angiogenssis is truly

inhibited (see Moses Biotech 9:630-634, 1991; page 631, line col.2 para.3, para.6).). In instant case the specification as filed fails to provide any evidence that establishes that nucleic acid as claimed encodes a polypeptide that has any anti-angiogenic activity (in-vivo).

In addition, the scope of invention as claimed encompasses variants of nucleotide sequences encoding a canine endostatin-like activity. The variations as claimed encompasses the conserved motifs that are germane to the endostatin-like biological activity. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Therefore, the asserted use for the claimed invention is not supported by either a specific and/or substantial utility, since no function could be ascribed to the gene product.

The instant specification does not comply with 35 U.S.C. 101 and 112 since nebulous expressions "biological activity" and "biological properties" do not contain a sufficiently explicit indication of usefulness of compounds and how to use them. The utility requirements must be met at the time of filing and not after someone else identify a utility that had not been disclosed in the specification. The disclosure is insufficient where experimentation is necessary to determine actual uses, or possible lack of uses, of compounds, as well as how to employ them in a useful manner. For example, it cannot be presumed that a steroid chemical compound is "useful" under 35 U.S.C. 101, or that one skilled in the art will know "how to use" it, simply because compound is closely related only in a structural sense to other steroid compounds known to be useful (In re Kirk and Petrow, 153 USPQ 48 (CCPA 1967)). In instant case the mere presence of canine endostatin-like domain does not teach one skill in the art how to use the invention as claimed, since the disclosure is insufficient and requires further experimentation necessary to determine actual uses or possible lack of uses of the polypeptide, as well as how to

employ them in a useful manner. It cannot be presumed that any canine endostatin-like domain bearing polypeptide is useful under 35 USC 101/112 or that one skilled in the art will know "how to use" it, simply because polypeptide is closely related only in a structural sense to other endostatin-like proteins known to be useful.

In view of the foregoing, one skilled in the art would not readily attribute any particular canine endostatin-like activity encoded by the claimed nucleic acid sequence or variants thereof in view of the low sequence similarity and the lack of sequence conservation therein. Therefore, the asserted use for the claimed invention is not supported by either a specific and/or substantial utility, since no function can be ascribed to the gene product. The only immediate apparent utility for the instant invention would be further scientific characterization of the claimed amino acid sequences a putative canine endostatin-like activity.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

Invention relates to nucleic acid sequence that encodes an endostatin.

Breadth of Claims and Guidance Provided in the Specification

The instant claims are drawn to an isolated DNA sequence, which encodes an endostatin-like polypeptide. The specification asserts the present invention relates to novel polynucleotide sequences, which encode the angiogenesis inhibitor endostatin, and more particularly, the canine angiogenesis inhibitor (spec. page 1, para.1). At best the specification teaches that addition of proposed canine-endostatin polypeptide inhibited the stimulating effect to of bFGF on CPAE cells **in-vitro** (spec. page 72). The specification fails to disclose that nucleic acid sequences as claimed encodes a polypeptide that inhibit angiogenesis in a canine.

State of Art and Predictability

The state of antiangiogenesis art is in very early stages of development. The tumor blood vessels proliferate 20-2000 times faster than any normal endothelium in an adult as the result hypoxia and variety of other uncharacterized stimuli. The net balance of pro and anti-angiogenic factors determine, whether new blood vessels are formed or not. Furthermore, not all parts of growing solid tumors participate in angiogenesis at the same time due to complex network of cytokines and angiogenic factors produced in a tumor. There are significant inter and inter-species variations in the tumor cell and tumor blood vessel micoenviornment, therefore great care be taken in the extrapolation of in-vitro data to a in-vivo situation. More information on target epitopes density and distribution and coagulation status in experimental animal and cancer patients is required for the proper interpretations (Molema et al, Biochem, Pharmcol. 55:1939-45, 1999, see page 1941, 1993 col.1). Angiogenesis is multi factorial process that involves degradation of basement membrane, migration and proliferation of capillary EC cells and formation of three-dimensional capillary tubes. In-vitro cell migration assay is mere a prescreening method that further requires testing in a standard in-vivo model. The state of art at the time of filing concluded that although number of factors have been studied in-vitro which can interfere with one or more of the steps required for angiogenesis, it is essential to test these substances using in-vivo assay to ensure that angiogenssis is truly inhibited (Moses Biotech 9:630-634, 1991; page 631, line col.2 para.3, para.6).). In instant case the specification as filed fails to provide any evidence that establishes that nucleic acid as claimed encodes a polypeptides that has any anti-angiogenic activity (in-vivo) explicitly or implicitly as putatively considered by the invention as claimed.

In addition, the scope of invention as claimed encompasses variants of nucleotide sequences encoding a canine endostatin-like activity. The variations as claimed encompasses the conserved motifs that are germane to the endostatin-like biological activity. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide

must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). The courts have clearly stated that: a specification need not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".* Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). Therefore, considering the limited disclosure and the state of the art one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 4-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claims are drawn to an isolated nucleic acid sequences (encoding an endostatin) which hybridizes to the complement of SEQ ID NO: 1 and 3 under high and moderate stringency conditions. At best the specification discloses only one variant of SEQ ID NO:1 and SEQ ID

NO:3 each that encodes a canine endostatin. The scope of invention as claimed encompasses any variant of SEQ ID NO:1 and 3 which encodes an endostatin obtained from any organism (except chicken, human or mouse). The variants as claimed encompasses substitution, addition and/or deletion of any nucleic acid sequences in SEQ ID NO:1 and 3. The specification fails to disclose any variant of SEQ ID NO:1 or 3 obtained from any other organism that encodes an endostatin-like activity explicitly or implicitly as putatively considered by the invention as claimed.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only teaches canine-endostatin but fails to disclose any variant of SEQ ID NO:1 or 3 obtained from any other organism that has the functional property of endostatin polypeptide explicitly or implicitly. The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the nucleic acid variants (as claimed) has been defined only by a statement of function that broadly encompasses an endostatin-like activity, which conveyed no

distinguishing information about the identity of the claimed DNA sequence, such as its relevant structural or physical characteristics. The variation as claimed also encompasses the conserved motifs, which are considered germane to the functional activity of an endostatin-like polypeptide. The variation as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Kin-Ming et al (US20030139365A1, 2003).

The scope of invention as claimed encompasses an isolated nucleic acid sequence that hybridizes to the complement of SEQ ID NO:1 and 3 of instant application.

Kin-Ming teaches isolated nucleic acid sequences obtained from dog (SEQ ID NO:34) which have 63.8% and 95.3% similarity with the nucleic acid sequence of SEQ ID NO:1 and 3 of instant application. In addition the cited art teaches that SEQ ID NO:34 encodes canine endostatin (page10 example 7-9). Thus the cited art clearly anticipate the invention as claimed.

Claims 4-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Holaday et al (US20030012792A1, 2003).

The scope of invention as claimed encompasses an isolated nucleic acid sequence that hybridizes to the complement of SEQ ID NO:1 and 3 of instant application.

Holaday teaches isolated nucleic acid sequences obtained from dog (SEQ ID NO:50) which have 63.8% and 95.3% similarity with the nucleic acid sequence of SEQ ID NO:1 and 3 of instant application. The cited art clearly anticipate the invention as claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02. Thus the cited art clearly anticipate the invention as claimed

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER

JEFFREY FREDMAN
PRIMARY EXAMINER